

AperTO - Archivio Istituzionale Open Access dell'Università di Torino

The prenylation inhibitor, lonafarnib: A new therapeutic strategy against hepatitis delta

This is a pre print version of the following article:

Original Citation:

Availability:

This version is available <http://hdl.handle.net/2318/1571853> since 2016-06-24T17:50:50Z

Published version:

DOI:10.1016/S1473-3099(15)00155-3

Terms of use:

Open Access

Anyone can freely access the full text of works made available as "Open Access". Works made available under a Creative Commons license can be used according to the terms and conditions of said license. Use of all other works requires consent of the right holder (author or publisher) if not exempted from copyright protection by the applicable law.

(Article begins on next page)

This Accepted Author Manuscript (AAM) is copyrighted and published by Elsevier. It is posted here by agreement between Elsevier and the University of Turin. Changes resulting from the publishing process - such as editing, corrections, structural formatting, and other quality control mechanisms - may not be reflected in this version of the text. The definitive version of the text was subsequently published in THE LANCET INFECTIOUS DISEASES, 15 (10), 2015, 10.1016/S1473-3099(15)00155-3.

You may download, copy and otherwise use the AAM for non-commercial purposes provided that your license is limited by the following restrictions:

- (1) You may use this AAM for non-commercial purposes only under the terms of the CC-BY-NC-ND license.
- (2) The integrity of the work and identification of the author, copyright owner, and publisher must be preserved in any copy.
- (3) You must attribute this AAM in the following format: Creative Commons BY-NC-ND license (<http://creativecommons.org/licenses/by-nc-nd/4.0/deed.en>), 10.1016/S1473-3099(15)00155-3

The publisher's version is available at:

<http://linkinghub.elsevier.com/retrieve/pii/S1473309915001553>

When citing, please refer to the published version.

Link to this full text:

<http://hdl.handle.net/2318/1571853>

Comment

The prenylation inhibitor, lonafarnib: a new therapeutic strategy against hepatitis delta

Mario Rizzetto, Alessia Ciancio

Refers To

Christopher Koh, Laetitia Canini, Harel Dahari, Xiongce Zhao, Susan L Uprichard, Vanessa Haynes-Williams, Mark A Winters, Gitanjali Subramanya, Stewart L Cooper, Peter Pinto, Erin F Wolff, Rachel Bishop, Ma Ai Thanda Han, Scott J Cotler, David E Kleiner, Onur Keskin, Ramazan Idilman, Cihan Yurdaydin, Jeffrey S Glenn, Theo Heller **Oral prenylation inhibition with lonafarnib in chronic hepatitis D infection: a proof-of-concept randomised, double-blind, placebo-controlled phase 2A trial** *The Lancet Infectious Diseases*, Volume 15, Issue 10, October 2015, Pages 1167-1174

Chronic hepatitis delta is a severe liver disease occurring in carriers of the hepatitis B surface antigen (HBsAg) superinfected with the hepatitis delta virus (HDV);¹ this is the smallest virus in human virology with a genome of about 1700 nucleotides coding for a single protein, the hepatitis delta antigen (HDAg) of 195 aminoacids.²

With the implementation of HBV vaccination, HDV infection has diminished in developed countries but its endemicity remains high in many low-income countries of Asia, Africa, and the Amazon basin.³

Treatment still relies on interferon, first introduced empirically in the 1980s, but results are limited.⁴ Therapy is problematic because the minimalist HDV does not encode for any enzymatic function and has no replicative machinery of its own to be targeted by antivirals; it is replicated by host RNA polymerases deceived to recognise the viral RNA as if it were cellular DNA.⁵ The only help required from HBV is the HBsAg coat whereby the HDV attaches to hepatocytes and assembles in the virion. Unsurprisingly, antivirals such as lamivudine, adefovir, and entecavir that effectively decrease HBV-DNA levels but leave HBsAg unaffected, failed to control HDV.⁶

The native HDAg (small HDAg) is elongated to a large HDAg by a cellular adenosine deaminase. Further post-translational modifications of the two antigenic isoforms by host enzymes regulate the various steps that drive the life-cycle of the HDV within the cell;⁷ prenylation of the last four aminoacids of the large HDAg (the so called CXXX box) is required for the interaction of the HDAg with the HBsAg to form the virion.⁸

The crucial role of prenylation has led to the hypothesis that disruption of this post-translational modification by drugs could prevent virion morphogenesis and provide a cure for hepatitis delta. The prenyl-lipid on the HDAg is farnesyl and farnesyltransferase inhibitors targeting the transfer of farnesyl to the large HDAg were used with success in vitro and in the mouse model to diminish HDV release.⁹

In this issue of *The Lancet Infectious Diseases*, Christopher Koh and colleagues¹⁰ provide the results of a first attempt to use the prenylation inhibitor lonafarnib in human HDV disease. Patients with HBsAg-positive chronic hepatitis delta and a Ishak fibrosis score of 3, all HBeAg negative with only borderline HBV-DNA in serum and a median 9.27×10^5 IU ml HDV-RNA, were randomised to two groups of six patients receiving lonafarnib 200 mg or 400 mg daily in two doses for 28 days, with a placebo control of two patients in each group.

By the end of therapy serum HDV-RNA had declined by 0.73 log with the lower dose of lonafarnib and by 1.54 log with the higher dose of lonafarnib; declines were significantly different compared with placebo.

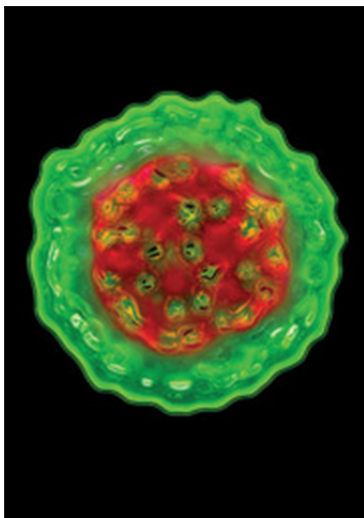
Serum HBsAg and aminotransferases did not change, and HDV-RNA returned in all patients to baseline after discontinuing therapy.

Koh and colleagues¹⁰ provide the first proof-of-concept that a prenylation inhibitor can decrease HDV in a dose-dependent manner and indicate a new unconventional strategy to attack a virus resistant to conventional therapies. Of note, no HDV mutations associated with lonafarnib non-response were detected in the study by population-based sequencing for the large HDAg; thus depriving the HDV access to a crucial host function challenges the highly mutagenic HDV to develop resistance, as the relevant genetics are not under its control.

In clinical practice, several problems need to be considered before lonafarnib becomes a therapeutic option in human HDV disease.

In the context of the HBsAg carrier, HDV remains infectious and ready to reactivate even at very low titers.¹¹ Thus, the decline pattern of serum HDV-RNA noted in the study, exhibiting a plateau phase in the second part of treatment, seems ephemeral and higher dosages of lonafarnib, longer therapy, or both, seem necessary to significantly diminish HDV. This however raises a problem of tolerance: with the most effective 400 mg dosage of the drug all patients had gastrointestinal symptoms (intermittent vomiting in 50%) and weight loss (mean 4 kg).

Further studies are needed to establish the role of lonafarnib in human HDV disease; rather than using lonafarnib as a single therapy for treating hepatitis delta, this drug might prove an important partner in combined therapies with novel agents such as myrcludex B¹² or nuclei acid polymers,¹³ aimed at preventing entry of the hepatitis delta virion into hepatocytes or at reducing HBsAg particles.



References

1

M Rizzetto

Hepatitis D: thirty years after

J Hepatol, 50 (2009), pp. 1043–1050

2

JM Taylor

Structure and replication of hepatitis delta virus RNA

Curr Top Microbiol Immunol, 307 (2006), pp. 1–23

3

M Rizzetto, A Ciancio

Epidemiology of hepatitis D

Semin Liver Dis, 32 (2012), pp. 211–219

4

A Ciancio, M Rizzetto

Chronic hepatitis D at a standstill: where do we go from here?

Nat Rev Gastroenterol Hepatol, 11 (2014), pp. 68–71

5

JM Taylor

Chapter 3. Replication of the hepatitis delta virus RNA genome

Adv Virus Res, 74 (2009), pp. 103–121

6

C Yurdaydin

Treatment of chronic delta hepatitis

Semin Liver Dis, 32 (2012), pp. 237–244

7

WH Huang, CW Chen, HL Wu, PJ Chen

Post-translational modification of delta antigen of hepatitis D virus

Curr Top Microbiol Immunol, 307 (2006), pp. 91–112

8

JS Glenn, JA Watson, CM Havel, JM White

Identification of a prenylation site in delta virus large antigen

Science, 256 (1992), pp. 1331–1333

9

JS Glenn, JC Marsters Jr, HB Greenberg

Use of a prenylation inhibitor as a novel antiviral agent

J Virol, 72 (1998), pp. 9303–9306

10

C Koh, L Canini, H Dahari, et al.

Oral prenylation inhibition with lonafarnib in chronic hepatitis D infection: a proof-of-concept randomised, double-blind, placebo-controlled phase 2A trial

Lancet Infect Dis (2015) published online July 17.

11

A Ciancio, M Rizzetto

PEG-IFN for the treatment of hepatitis D

Nat Rev Gastroenterol Hepatol, 8 (2011), pp. 304–306

12

S Urban, R Bartenschlager, R Kubitz, F Zoulim

Strategies to inhibit entry of HBV and HDV into hepatocytes

Gastroenterology, 147 (2014), pp. 48–64

13

M Bazinet, V Pantea, V Cebotarescu, et al.

Significant reduction of HBsAg and HDV-RNA by the nucleic acid polymer REP-2139 in Caucasian patients with chronic HBV/HDV co-infection

J Hepatol, 62 (2015), p. 257